PATENT COOPERATION TREATY

Rec'd PCT/PTO 16 MAY 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	10.03.2005
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
21518 WO-HIL	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/13545	02.12.2003	06.12.2002

Applicant
ROCHE DIAGNOSTICS GMBH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Wallentin, M Tel. +31 70 340-3991

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 21518 WO-HIL	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13545	International filing date *(day/month/year)* 02.12.2003	Priority date *(day/month/year)* 06.12.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/14		
Applicant ROCHE DIAGNOSTICS GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.07.2004	10.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Vadot-Van Geldre, E Telephone No. +31 70 340-1973

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13545

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-32 as originally filed

Sequence listings part of the description, Pages

1-4 received on 26.02.2004 with letter of 23.02.2004

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	1-5,7-9,10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents :

D1 : Edwards et al, 2001. J Clin Micr, 39(9), 3047-3051.
D2 : Conolly et al, 09-2002. Int J Sys Evol Micr, 52(5), 1837-1843.
D3 : Sloan et al, 05-2002. Abstr. AMS, 102, 143.
D4 : Niemeyer et al, 1999. Abs Interscience conference on Antimicrobial Agents and Chemotherapy, 39, 208.
D5 : US5849488

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The subject-matter of claims 1-5,7-9,10 does not meet the criteria of Article 33(2) PCT having regard to novelty.

1.1 D1 (abstract ; figure 1 ; table 1) discloses a method for identification of Staphylococci, including S. aureus, using PCR amplification and melting curve analysis. Primers and probes are designed from the variable regions of the 16S rRNA gene. Consequently, D1 is prejudicial to the novelty of claims 1-2, 4-5,7-9. It was argued that the present method, as opposed to D1 (pg 3050, left col, first par), did not lead to false positive results. However, step bba) fails to identify the technical features necessary to avoid such false results and defines the subject-matter as a result to be achieved.

1.2. D2 (abstract) discloses a method for the detection and identification of gram positive bacteria comprising PCR amplification of the 16S region and fluorescence based melting curve analysis using a pair of FRET-probes. Consequently, D2 is prejucidial to the novelty of claims 1-4,7. The fact that the method of D2 cannot be used to perform a specific species identification does not constitute a difference with the above mentioned claims. Indeed, the claimed method is also aimed at the identification of a subset of organisms, like eg. species belonging to the genera of Caloramator. Furthermore, D2 also allows identification of specific bacteria, namely F. nodosum and F. gondvanense.

1.3. D3 (abstract) and D4 (abstract) disclose methods for the detection of respectively vancomycin resistance in Enterococci and meticillin resistance in Staphylococci using PCR and fluorescence based metling curve analysis. Since the same LightCycler® as in present application is used, the hybridisation probes used must also be labelled with

FRET partners. Even if both methods are aimed at the identification of antibiotic resistance genes, the implicit outcome of the methods will be identification of the subset of bacteria that are vancomycin resistent or meticillin resistent, respectively. Therefore, D3 and D4 anticipate the novelty of claims 1-5,7-8.

1.4. D5 (claims ; examples 2-3) discloses a kit for the identification of Streptococcus and Staphylococcus containing primers capable of amplifying the 16S-23S rRNA spacer regions of said bacteria. Consequently, D5 anticipates the novelty of claim 10. The fact that the kit disclosed by D5 does not contain reagents for amplification and detection of Enterococcus rRNA spacer sequences is not of relevance, because the kit of claim 10 does not necessarily contain the 3 primer-sets for the rRNA spacer region of Enterococcus, Staphylococcus and Streptococcus.
As a matter of completeness it is specified that even if the kit of claim 1 would be limited to the presence of all the primer-sets for the 3 pathogenic bacteria listed, inventive step objections still would arise (Art. 33(3) PCT), because it lies within the knowlegde and ability of the skilled person to design primers capable of amplifying the 16S-23S rRNA region of any target bacterium.

2. The dependent claim 6 does not contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of Art. 33(3) PCT with respect to inventive step. The use of "an rRNA spacer region" such as the 16S-23S spacer region is considered as an obvious alternative since it is well known to the skilled person that this region shows a wide sequence divergence in bacteria which is advantageous for design of probe-panels (see eg. D5). Therefore, the subject-matter of claim 6 does not involve an inventive step.

3. The claims meet the criteria of Article 33(4) PCT with regard to industrial applicability.

Additional remarks :

1. The steps bba) and bbb) in claim 1 use vague terms which fail to distinguish the subject-matter from routine optimization protocols belonging to daily routine in research laboratories. Even PCR falls under the scope of this expression since hybridisation at a pre-selected temperature and dependence on the temperature is subsequently monitored by the presence or absence of a PCR product via gelelectrophoresis. The steps lack technical features and fail to identify the method to which they attempt to refer, namely "melting curve analysis" (see examples of present application). A general

lack of clarity results therefrom which entails general Art. 33(2) PCT objections. However, for the examination of present application the above mentioned steps have already been read and interpreted in the light of the description as referring to "melting curve analysis" (see above). However, this does not exclude the necessity to use a more appropriate definition of steps bba) and bbb) in claim 1 in order to avoid said general Art. 33(2) PCT objections.

2. Terms and expressions as "pre-selected nucleic acid sequence region" (eg. claim 1), "predetermined sub-group of pathogenic Gram positive bacteria" (eg. claim 1) are vague and leave the skilled person in doubt about the technical features to which they refer (Art. 6 PCT).